DETAILED ACTION

During the pre-appeal conference on 02/23/2010, it was agreed that the rejections of record are deficient in that they do not address exposure of a biosystem (e.g., cells, or organism) to herbal composition of interest.

Consequently, finality of the preceding office action is withdrawn, and the following rejections are applied.

Status of Claims

Claims 83,84,87-89 are pending.

Claim Rejections - 35 USC § 103.

Claims 83,84,87-89 are rejected under 35 U.S.C. 103(a) as unpatentable over McLaughlin (Drug Information Journal, vol. 32, pp 513-521, 1998) and Khwaja et al (US Patent 6113907) in view of Kojima et al. (Biol. Pharm Bull, 21(4),426-428; reference provided in IDS), Wallace et al (Molecular Medicine Today. Volume 3, Issue 9, September 1997, pages 384-389), Friend et al (US Patent 6,218,122), and Xiong et al. (Molecular Breeding 4: 129–136, 1998).

The claims are directed to quality control method for assessing the equivalency of a test and standardized batches a herbal composition by exposing a biosystem (e.g., cells, or tissue, or an organism) to either standardized or test batches of the herbal composition, determining differential gene expression in the biosystem (as compared to

untreated control), and comparing the differential gene expression values obtained for the test and standardized batches.

McLaughlin et al. teach that bioassays offer a special advantage in the standardization and quality control of heterogeneous botanical products. Such products can be "heterogeneous" due to the presence of mixtures of bioactive components either from the same or from purposefully mixed botanical sources. McLaughlin describes several bioassays, such as brine shrimp lethality test, inhibition of crown gall tumors assay, inhibition proliferation assay, etc. (see Abstract), relative potency of the test *vs.* control herbal composition was determined (see, for example, p. 522 describing seasonal variations in the potency of botanical preparation).

McLaughlin does not teach using genomic-based bioassay to determine the effect of a herbal composition, and does not specifically address control samples as "standardized".

Khwaja et al teaches method for quality control of herbal compositions by fingerprinting effects of herbal compositions in bioassays to provide reproducible material in the predictable and consistent treatment of patients (column 2, lines 39-51). The reference teaches that use of bioassays is necessary for ensuring quality of a botanical product.

Complex plant materials and extracts exist which have potent, but relatively unpredictable, medicinal properties. These materials are, for the most part, useless in a clinical setting because of the inherent risks involved with treating patients with poorly characterized materials which have no established batch consistency and which may differ widely in composition. Accordingly, there is a need to provide methods for standardizing such complex botanical materials

The method of Khwaja et al. comprises harvesting botanical material (whole or part), determining standardized bioactivity profile, comparing the calculated bioactivity of the botanical composition to a bioactivity fingerprint standard, and determine whether the botanical material is a pharmaceutical grade St. John's Wort (column 9, bottom). The "biosystems" (as they are addressed in the instant claims) in Khwaja can be selected by an artisan depending on the nature of fingerprint desired; for example, they can be cells, tissues, or whole organisms (see cols 22, section 5.4; col.23, lines 24-26; col. 2, section 5.4.2). The herbal compositions tested are derived from a whole plant or parts thereof (see col. 16, line 51), and overall activity of the preparation is determined (col. 16, line 60). If the quantitative fingerprint of the sample falls within the range of quantities set forth for the pharmaceutical grade fingerprint, then the material is identified a pharmaceutical grade (col. 17, lines 46-49).

Thus, Khwaja reads on assessing the equivalency of a test and standardized batches a herbal composition by exposing a biosystem (e.g., cells, or tissue, or an organism) to either standardized or test batches of the herbal composition, assaying reaction of the biosystem, and comparing the quantitative measures of the response of the biosystem to the test and standardized batches.

Khwaja, as McLaughlin, does not teach "genomic-based" bioassay. However, Khwaja addresses determining differential expression of proteins, such as assaying decreased expression of reverse transcriptase in cell culture (col. 26, section 5.4.4). [1]

[1] Similarly, Hylands et al (US 6806090) teaches method for quality control and standardization of medicinal plant products comprising preparing solutions or extracts of standard and test samples of whole plant product and comparing them using one or more biological profiling techniques, such as

Unlike the instant method, Khwaja addresses differential expression of a protein, rather than of a gene.

Kojima et al. teach determination of differential expression of genes resulting from exposure of "biosystem" (mice) to a Japanese herb preparation (see Abstract , p. 426) .

The basic concept of generating and comparing expression profiles, including gene expression profiles, to known profiles for the purpose of determining drug effectiveness is well known. Wallace et al teaches that DNA chips is a major advance in testing complex mixtures which provide much faster and more reliable assay. See Abstract and throughout the reference. Friend et al (U.S. Pat. No. 6,218,122) teaches determining the effect of a drug therapy upon a subject by comparing a diagnostic gene expression profile from a subject undergoing a therapy with an "interpolated perturbation response profile" for that therapy. The interpolated perturbation response profile which is most similar to the diagnostic profile indicates the level of effect or drug dose level. Xiong et al. teaches differential gene expression profile of the whole batch of plant extract via a genomic-based bioassay. See Abstract

Taken together, using the known technique of gene array analysis of differential gene expression as a bioassay used for a quality control method instead of other types of bioassays used the methods of McLaughlin or Khwaja et al would have been obvious to one of ordinary skill. The nature of the problem to be solved –

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proteomic analysis. See Example 6 describing effect of Buddleja globosa on protein expression in human

comparison between herbal compositions for the purpose of quality control may lead inventors to look at references relating to new and improved methods of assaying bioequivalence of herbal compositions. Therefore, it would have been obvious to use the more advanced method of gene expression analysis described, for example in Wallace, Xiong, or Wallace. As one skilled in the botanical art was aware of importance of understanding of gene expression for quality control, using the known technique gene expression analysis to provide the desired information for the quality control would have been obvious to one of ordinary skill.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571)272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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dermal fibroblast cells.

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/Michael Borin/
Primary Examiner, Art Unit 1631

mlb